UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

LICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,475	10/10/2001	Ryuichi Morishita	6235-59221	4309

24197 7590 09/17/2004

KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/17/2004

e find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,475	MORISHITA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9,11,12,14,16,22-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,11,12,14,16,22-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/13/04 has been entered.

Claims 9, 11, 12, 14, 16, 22-43 are pending.

Applicants' traversal, the amendment to the specification, the amendment to claim 9 and the addition of claims 22-43 in paper filed on 7/13/04 is acknowledged and considered.

Election/Restrictions

The instant application contains species in claim 11 and new claims 24, 32, and 40 drawn to nonelected species with traverse in paper filed on 7/7/02.

Claim Objections

Claim 9 is objected to because of the following informalities: the term [[a]] on line 2 before the word "nucleic acid" has been removed from claim 9 and there is nothing to indicate that the term has been removed. In the response to this instant office action Applicants are reminded to follow revised 37 CFR 1.121. See 68 Fed. Reg. 38611 (June 30, 2003) or website www.uspto.gov/web/patents/ifw/. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 22, and 27-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The new claims 28-43 are not supported by the as-filed specification. There appears to be no written description of a method of increasing the mRNA level of ETS-1 in a muscle of a subject comprising administering a therapeutically effective amount of a nucleic acid encoding HGF to the muscle of the subject or a method for increasing the level of MMP-1 in a muscle of subject in the application as filed. See MPEP § 2163.06. Page 5, line 17, to page 9, line 36 and page 12, line 30 to page 13, line 30 cited for support of the new claims by applicants do not disclose either method. On pages 12 and 13, the applicants teach the influence of glucose concentration and HGF addition against MMP-I production of the angioendothelial cell in vitro and effect of HGF against angioendothelial cells *in vitro* (Changes of transcription factor ETS-I related to angiogenesis). The method claims are directed to in vivo methods of increasing mRNA level of ETS and levels of MMP-1 in a muscle of subject. The claims are broader than the teachings in the specification directed to treating subject with a diabetic ischemic disease

using a nucleic acid encoding HGF. The specification does not describe that increasing mRNA level of ETS-1 or level of MMP-1 in angioendothelial cells in vitro would support claims directed to increasing ETS or MMP1 in a muscle in vivo. There are a variety of cells in the muscle including angioendothelial cells in blood vessels that traverse a muscle and different cells that make a muscle have different regulation factors. The teaching in the specification by the applicants of increasing of ETS and MMP1 obtained in angioendothelial cell in vitro does not support a method for increasing these transcription factors in a muscle in vivo. Thus, there is nothing in the examples on these pages that supports the in vivo methods set forth in the new claims.

With respect to claim 22, the limitation "every three or every five weeks" is not supported the specification. Applicants cite page 9, lines 32-36, page 11, line 32 to page 12, line 15page 14, lines 1-4 for support of the new claim. On page 9, the applicants contemplate range of dosage and amount of time the agent can be administered. On pages 11 and 12, the applicants teach administering a nucleic acid encoding HGF (50μg) once into rats. On page 14, the applicants teach that therapeutic agent can be administered more than once. The specification does not provide support for the limitation because there is nothing in the specification that would lead one skilled in the art administering the nucleic acid every three to five weeks. Therefore, there is nothing in the specification that supports the limitation as set forth in new claim 22.

In addition, amended claim 16 and newly filed claims 27, 35, and 43 are not supported by the as-filed specification. There appears to be no written description of a method for the treatment of diabetic ischemic disease in a subject comprising administering a nucleic acid

encoding HGF once every few weeks or once every few days, wherein at least 50μg of the nucleic is administered to the subject in the application as filed. There is not page cited for support of the claims. See MPEP § 2163.06. The only part of the specification that might be associated with the claims is found on page 9, lines 28-36 and page 12, experiment 1. On page 9, the applicants contemplate range of dosage and amount of time the agent can be administered. On page 12, the applicants teach administering a nucleic acid encoding HGF (50μg) once into rats. The specification does not lead one skilled in the art to administering a nucleic acid encoding HGF (50μg) every few weeks or once every few days or into animals other than rats. Citing the working example on page 12 in the specification as file for support of the claimed methods, as now recited, is overreaching because the instant specification does not disclose that administering 50μg is a general teaching that is generally applicable to the claimed methods. Therefore, there is nothing in the specification that supports the in vivo methods as set forth in the claims.

"It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose." *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997).

It is apparent that the applicants at the time the invention was made did not intend or contemplate using the methods cited in the claims as part of the disclosure of their invention. There is no evidence in the specification that the applicants were in possession of the claimed methods as set forth in the claims 16 and 22-43, as it is now claimed, at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32, 33, 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32, 33, 40, and 41 recite the limitation "the diabetic ischemic disease" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. The claims from which these claims depend from do not recite a diabetic ischemic disease.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 9, 11, 12, and 14 remain and claims 23-26, 28-34, and 36-42 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Morishita et al. (US 6,248,722) in view of Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cited on an IDS).

Morishita teaches a method of nucleic acid therapy for treating a disease in a subject for which hepatocyte growth factor (HGF) is effective, comprising administering to the muscle of the subject a HVJ-liposome comprising HGF (column 14). Morishita teaches that HGF can treat arterial diseases (column 4, lines 35-49). Furthermore, Morishita teaches that the dose may be divided into several days or few months, which would anticipate delivering the nucleic acid several times to the subject, e.g., once every few weeks, once every few days (column 6, lines 53-54). The pathology of an ischemic disease in a subject results in poor circulation in an affected area (e.g. lower limb, heart, brain) of the subject. HGF gene therapy results in increase circulation of blood in the affected area of the subject. The art of record indicates that there are only a few types of ischemic diseases. Thus, one skilled in the art would have anticipated that using HGF gene therapy to treat an ischemic disease in a subject taught by Morishita would embrace treating diabetic ischemic disease in the lower limb of a subject with the disease. In addition, the method steps taught by Morishita anticipate the methods recited in claims 28-34 and 36-42 because Morishita teaches the same method steps, which would result in one skilled in the art, absence evidence to the contrary, observing an increase in mRNA level of ETS-1 in a muscle of a subject or an increase of MMP-1 in a muscle of a subject.

In addition, Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section teaches that arteriosclerosis bitterns is a lower limb arteriosclerosis caused by diabetes mellitus resulting in the aggravation in blood circulation followed by lower limb necrosis or gangrene. A scientist, Dr. Ogihara, was cited in the Japan Financial News Paper, Local News Section and he states that, "the HGF has a more potent angiogenesis activity and less side effects than VEGF." Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section further teaches that, "a gene encoding the HGF having angiogenesis activity is introduced into a special circular gene, a plasmid, followed by injection to a muscle around the affected part in the patient." Thus, one of ordinary skill in the art would have been motivated as obvious over Morishita in view of Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) to treat diabetic lower limb ischemic disease in a subject using HGF nucleic acid therapy since diabetic lower limb ischemic disease results in lower limb arteriosclerosis and HGF gene therapy can be used to regenerate new vasculars in an affected of the subject.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Applicant's arguments filed 7/13/04 have been fully considered but they are not persuasive because the claimed methods are still anticipated by Morishita.

Applicants argue that '722 patent does not teach nor render obvious, intermittent repeated doses of HGF, such that a specific amount is administered to a subject every few days or every few weeks.

Applicants' argument is not found persuasive because the claims do not recite using a specified amount of HGF every few days or every few weeks. In addition, Morishita teaches that the dose may be divided into several days or few months, which would anticipate once every few weeks or once every few days because there is no definition in the disclosure for the term "every few weeks" or "few days" (column 6, lines 53-54).

Applicants further argue that unexpectedly superior results in the treatment of diabetic ischemic rebut any *prima facie* case of obviousness asserted against rejected claims.

Applicants' argument is not found persuasive because other than the assertion by applicants, the applicants provide no guidance and/or evidence to support the assertion. Therefore, applicants' assertion regarding the "superior results" is not compelling. See MPEP 716.01(c) II.

Double Patenting

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

There was a provisional obvious double patenting rejection in office action mailed on 10/13/02 over claims from co-pending application 09/857,719. The rejection was overcome because applicants cancelled the claims that were cited in the provisional double patenting rejection. However, in view of the addition of claim 36 in co-pending application '719. A new provisional obviousness double patenting rejection follows:

Claims 9, 14, 23, 26, 28, 29, 30, 31, 34, 36, 37, 38, 39, and 42 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 36 of copending Application No. 09/857,719 in view of Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) (cite on an PTO-1149).

The instant claims are directed to a method of treating a diabetic ischemic disease in a subject comprising administering an HVJ-liposome comprising a nucleic acid encoding HGF to the muscle of an ischemic site, wherein the nucleic acid is administered to the subject once every few weeks. In addition, the instant claims recite a method for increasing mRNA levels of ETS-1 in a muscle or increasing the level of MMP-1 in muscle using the method described above.

Claims from application '719 are directed to a method of treating a disorder comprising administering an HVJ-liposome comprising a nucleic acid encoding HGF into an affected part of tissue using echocardiography. The claims from '719 do not specifically recite treating a diabetic ischemic disease and administering the nucleic acid to the subject once every few weeks. In addition, the claims from '719 do not specifically recite a method for increasing mRNA levels of ETS-1 in a muscle or increasing the level of MMP-1 in muscle using the method described above. However, the specification of '719 teaches that the disorder can be an ischemic disease (page 2) and the nucleic acid can be administered once every few days or once every few weeks (page 9). In addition, the method steps for claims from '719 are the same method steps as recited in the instant claims 28, 29, 30, 31, 34, 36, 37, 38, 39, and 42. Thus, increasing the level of MMP1 or the mRNA level of ETS-1 would be an obvious result from the method steps from the claims of '719.

Furthermore, Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section teaches that arteriosclerosis bittern is a lower limb arteriosclerosis caused by diabetes mellitus resulting in the aggravation in blood circulation followed by lower limb necrosis or gangrene. A scientist, Dr. Ogihara, was cited in the Japan Financial News Paper, Local News Section and he states that, "the HGF has a more potent angiogenesis activity and less side effects than VEGF." Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section further teaches that, "a gene encoding the HGF having angiogenesis activity is introduced into a special circular gene, a plasmid, followed by injection to a muscle around the affected part in the patient." Thus, it would have been obvious in view of the claim from co-pending application '719 in view of

Gene Therapy of Osaka University, English translation from the Japan Financial News Paper, Local News Section (Dec. 14, 1998) for one of ordinary skill in the art to treat a diabetic ischemic disease in a subject using HGF nucleic acid therapy since diabetic ischemic disease results in arteriosclerosis and HGF gene therapy can be used to regenerate new vasculars in an affected of the subject.

This is a provisional obviousness-type double patenting rejection.

Claims 9, 14, 23, 26-31, 34, 36-39, and 42 directed to an invention not patentably distinct from claim 36 of commonly assigned US application 09/857,719. Specifically, see the reasons set forth above in the provisional double patenting rejection.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned US applications, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly

assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER